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Therapeutic Class Review
Incretin Mimetics

I. Overview

Exenatide is a recently developed agent that is structurally and pharmacologically different from the other antidiabetic agents and it was placed into a new drug class, the incretin mimetics, by the American Hospital Formulary Service (AHFS) in February 2007.[1-2] Exenatide mimics several actions of the endogenous incretin hormone, glucagon-like peptide-1 (GLP-1). GLP-1 is a peptide hormone that has several roles in the regulation of postprandial glucose levels and is secreted into the bloodstream in response to a meal. Exenatide binds to and activates GLP-1 receptors in the body and has the following actions:[3]

- Enhances glucose-dependent insulin secretion
- Suppresses glucagon secretion during periods of hyperglycemia
- Slows gastric emptying
- Reduces food intake

Table 1 lists the incretin mimetics included in this review. This review encompasses all dosage forms and strengths.

Table 1. Incretin Mimetics Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)
exenatide	injection	Byetta®

No generic products are available in this class.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines using the incretin mimetics are listed in Table 2. The International Diabetes Federation (IDF) diabetes treatment guidelines[4] do not incorporate exenatide into their recommendations; however, the recently published IDF guidelines for the management of postmeal glucose[5] include exenatide as an available treatment option, along with the α-glucosidase inhibitors, amylin analogs, dipeptidyl peptidase-4 (DPP-4) inhibitors, insulins and meglitinides for postmeal glucose management.

Table 2. Treatment Guidelines Using the Incretin Mimetics

Clinical Guideline	Recommendation(s)
American Diabetes Association (ADA): **Standards of Medical Care in Diabetes—2008**[6]	Prevention of Type 2 Diabetes • Metformin should be the only drug considered for use in diabetes prevention. For other drugs, issues of side effects and lack of persistence of effect in some studies led the panel to not recommend their use for diabetes prevention. • In addition to lifestyle counseling, metformin may be considered in those who are at very high risk and who are obese and under 60 years of age. Treatment of Type 2 Diabetes • Please see the following guideline (2006) and consensus statement update (2008) by the American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD).
American Diabetes Association	• The guideline states that α-glucosidase inhibitors, exenatide, meglitinides,

Clinical Guideline	Recommendation(s)
(ADA)/European Association for the Study of Diabetes (EASD): **Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy (2006)**[7]	and pramlintide were not included in the treatment algorithm due to their generally lower overall glucose-lowering effectiveness and limited clinical data. However, these agents may be appropriate in selected patients.
American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD): **Management of Hyperglycemia in Type 2 Diabetes Mellitus: A Consensus Algorithm for the Initiation and Adjustment of Therapy: Update Regarding the Thiazolidinediones (2008)**[8]	• The guideline states that α-glucosidase inhibitors, exenatide, meglitinides, pramlintide, and sitagliptin were not included in the treatment algorithm due to their generally lower overall glucose-lowering effectiveness and limited clinical data. However, these agents may be appropriate in selected patients.
American Association of Clinical Endocrinologists (AACE): **Medical Guidelines for Clinical Practice for the Management of Diabetes Mellitus (2007)**[9]	Diabetes Type 2 Patients Currently Treated Pharmacologically • Exenatide may be used with approved combinations of oral therapies in patients who have not achieved glycemic goals. • Exenatide has been approved as a supplement to monotherapy with metformin, a sulfonylurea, or a thiazolidinedione. The use of exenatide together with a sulfonylurea plus metformin is also approved. • Insulin therapy may be added to patients on maximum combination therapy (oral-oral, oral-exenatide) whose HbA_{1c} levels are 6.5%-8.5%.
American College of Endocrinologists (ACE)/American Association of Clinical Endocrinologists (AACE), Diabetes Road Map Task Force: **Road Maps to Achieve Glycemic Control in Type 2 Diabetes (2007)**[10]	Patients Naïve to Therapy • Exenatide is not listed as a first-line treatment option. • An incretin mimetic (exenatide) is listed as a treatment option in patients with an initial HbA_{1c} of 6%-10% and who are not achieving ACE recommended HbA_{1c} goals despite receiving maximally effective doses of a sulfonylurea and/or metformin or a thiazolidinedione. • Exenatide is not indicated for insulin-using patients. Treated Patients • To achieve glycemic goals in type 2 diabetics with a current HbA_{1c} of 6.5%-8.5%, an incretin mimetic (exenatide) may be added to metformin with or without a sulfonylurea or thiazolidinedione.
International Diabetes Federation (IDF) Clinical Guidelines Task Force: **Global Guideline for Type 2 Diabetes (2005)**[4]	• This guideline does not discuss the role of exenatide in the treatment of type 2 diabetes.
Institute for Clinical Systems Improvement (ICSI): **Healthcare Guideline: Management of Type 2 Diabetes Mellitus (2006)**[11]	• Metformin is the preferred oral agent unless contraindicated. Second-line agents are the sulfonylureas and glitazones (thiazolidinediones). • Exenatide may be used as an additional agent in combination with metformin, a sulfonylurea, or with metformin and a sulfonylurea in patients who have not achieved recommended glycemic control. • In regards to the weight gain associated with type 2 diabetes and its treatment, metformin, unless contraindicated, is recommended for most type 2 diabetic patients due to its weight benefits. Other agents associated with weight loss and maintenance includes acarbose, exenatide, and human amylin analogs. • Exenatide may be offered as an alternative option before starting insulin for patients on oral medication who are not achieving good blood sugar control.
National Institute for Health and	• This guideline does not discuss the role of exenatide in the treatment of type 2

Clinical Guideline	Recommendation(s)
Clinical Excellence (NICE): **Clinical Guidelines for Type 2 Diabetes: Management of Blood Glucose (2002)**[12]	diabetes.

III. Indications

Food and Drug Administration (FDA)-approved indications for the incretin mimetics are listed in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Incretin Mimetics[3]

Generic Name	FDA-Approved Indications
Exenatide	Indicated as adjunctive therapy to improve glycemic control in patients with type 2 diabetes mellitus who are taking metformin, a sulfonylurea, a thiazolidinedione, a combination of metformin and a sulfonylurea, or a combination of metformin and a thiazolidinedione, but have not achieved adequate glycemic control

IV. Pharmacokinetics

The pharmacokinetic parameters for the incretin mimetics are summarized in Table 4.

Table 4. Pharmacokinetic Parameters of the Incretin Mimetics[3,13]

Drug	Systemic Bioavailability	Protein Binding	Elimination	$T_{½}$ Elimination (hours)	Active Metabolites
Exenatide	Not reported*	Not reported	Renal	2.4	Not reported

*Human data is unavailable; however, in animal studies, bioavailability was observed at 65%-76%.

V. Drug Interactions

No specific serious drug interactions with exenatide have been reported by the manufacturer. Due to the slowing effect on gastric emptying, exenatide may delay the absorption of oral medications administered concomitantly. The manufacturer recommends that caution be used for oral medications that require rapid gastrointestinal absorption or require threshold concentrations for efficacy (eg, oral contraceptives, antibiotics). Agents that require threshold concentrations for efficacy should be taken 1 hour prior or 2 hours after exenatide administration.[3,13]

VI. Adverse Drug Events

The most common adverse reactions reported with the incretin mimetics are noted in Table 5. Patients on exenatide may develop anti-exenatide antibodies. In 30-week clinical trials, 38% of patients had developed low-titer antibodies by week 30. The level of glycosylated hemoglobin (HbA_{1c}) control was comparable to that observed in patients without antibody titers. In 6% of patients, a higher antibody level was detected and in 3% of the patients (half of the patients with high titers) glycemic responses appeared attenuated. Patients who developed anti-exenatide antibodies had similar rates and types of adverse events. Patients on exenatide therapy should be monitored for signs and symptoms of hypersensitivity reactions.[3]

In October 2007, the FDA published an alert regarding an association between exenatide and pancreatitis. This alert was based on a review of 30 postmarketing reports of acute pancreatitis in patients taking Byetta®. Twenty-seven of the 30 patients had a least one other risk factor for acute pancreatitis. Twenty-one patients were

hospitalized and 5 developed serious complications. In 6 patients, pancreatitis symptoms began or worsened soon after titration of the dose from 5 µg to 10 µg twice daily and 22 patients had improvement of symptoms after the discontinuation of Byetta® therapy. In 3 reports, symptoms of pancreatitis returned upon rechallenge with Byetta® therapy.[14] It is recommended that healthcare providers be aware of, and review with their patients the signs and symptoms of pancreatitis, including persistent severe abdominal pain which may be accompanied by nausea and vomiting. It is also recommended to discontinue Byetta® if pancreatitis is suspected.[14]

In August 2008, the FDA issued an update to this alert, referencing 6 cases of hemorrhagic or necrotizing pancreatitis – all reported prior to the update – in patients who had a history of Byetta® therapy; two patients subsequently died.

Exenatide is contraindicated in patients with a known hypersensitivity to exenatide or any component in Byetta®. Exenatide is not recommended for use in patients with gastrointestinal disorders or in patients with end-stage renal disease or renal impairment (creatinine clearance <30 mL/min).

Table 5. Adverse Events (%) Reported with the Incretin Mimetics[3,13]

Adverse Events	Exenatide
Cardiovascular	
Chest pain	✔
Central Nervous System	
Dizziness	9
Feeling jittery	9
Headache	9
Somnolence	✔
Dermatological/Allergic Reactions	
Anaphylactic reaction	✔
Angioedema	✔
Hyperhidrosis	<5
Hypersensitivity pneumonitis	✔
Injection site reaction	✔
Macular or papular rash	✔
Pruritus	✔
Urticaria	✔
Endocrine	
Hypoglycemia	14-36*
Pancreatitis	✔
Gastrointestinal	
Abdominal distention	✔
Abdominal pain	✔
Constipation	✔
Decreased appetite	<5
Diarrhea	13
Dysgeusia	✔
Dyspepsia	6
Eructation	✔
Flatulence	✔
Gastroesophageal reflux disease (GERD)	<5
Nausea	44
Renal failure	✔
Serum creatinine increased	✔
Vomiting	13
Neuromuscular and Skeletal	

Adverse Events	Exenatide
Weakness	<5
Other	
Anti-exenatide antibodies (low titers, high titers)	38, 6

✔ Percent not specified
*With concurrent sulfonylurea therapy

VII. Dosing and Administration

The usual dosing regimens for the incretin mimetics are summarized in Table 6.

Table 6. Usual Dosing for the Incretin Mimetics[3]

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Exenatide	Initial: 5 µg subcutaneously twice daily within 60 minutes before each of the two main meals of the day (approximately ≥6 hours apart) Maintenance: initial dose may be increased to 10 µg twice daily after 1 month of therapy	Safety and efficacy have not been established in pediatric patients.	Prefilled pen: 5 µg 10 µg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the incretin mimetics are summarized in Table 7. Exenatide has not been directly compared to any oral antidiabetic treatments available for type 2 diabetes. Also, the use of exenatide in conjunction with meglitinides or α-glucosidase inhibitors has not been studied.[1] The Food and Drug Administration (FDA) based their approval of exenatide on the results of the first three trials listed in Table 7. The five studies following these initial three trials are extension phase studies or a combination of results from the original three studies.

Table 7. Comparative Clinical Trials Using the Incretin Mimetics

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Buse, Henry et al[15] Exenatide 5 µg SQ BID in addition to their existing sulfonylurea therapy vs exenatide 5 µg SQ BID titrated to 10 µg BID after 4 weeks in addition to their existing sulfonylurea therapy vs placebo in addition to patients' existing sulfonylurea therapy	MC, PC, PG, RCT, TB Type 2 diabetic patients between the ages of 22 and 76 years, treated with maximally effective doses of a sulfonylurea (4 mg/day glimeperide, 20 mg/day glipizide, 10 mg/day glipizide XL, 10 mg/day glyburide, 6 mg/day micronized glyburide, 350 mg/day chlorpropamide, or 500 mg/day tolazamide) for at least 3 months, with fasting plasma glucose (FPG) <240 mg/dL, body mass index (BMI) 27-45 kg/m^2, HbA_{1c} 7.1%-11.0%, stable weight (± 10%) for 3 months prior to screening, no lab value >25% outside of normal value, and if female, who were postmenopausal, surgically sterile, or using	N=377 30 weeks	Primary: Change in HbA_{1c} Secondary: Change in FPG, weight, and fasting concentrations of insulin, proinsulin and lipoproteins	Primary: Significantly greater reductions in HbA_{1c} were noted with exenatide 10 µg (–0.86%) and exenatide 5 µg (–0.46%) vs placebo (+0.12%; P<0.0002 for pairwise comparison). Secondary: A significantly greater reduction in FPG was reported with exenatide 10 µg at week 30 vs placebo (–0.6 mmol/L vs +0.4 mmol/L; P<0.05). There was not a significant difference between the exenatide 5 µg and the placebo group (P value not reported). Significantly greater reduction in body weight was noted with exenatide 10 µg at week 30 vs placebo (–1.6 kg vs –0.6 kg; P<0.05). There was not a significant difference between the exenatide 5 µg and the placebo groups (P value not reported). There were no significant differences in fasting insulin concentrations between treatment groups (P value not reported). A significantly greater reduction in fasting proinsulin concentrations was noted with exenatide 10 µg at week 30 vs placebo (–16 mmol/L from baseline with exenatide 10 µg; P<0.01). A similar trend was reported with the exenatide 5 µg vs the placebo group, but significance was not reported (P value not reported). There was a small reduction in low-density lipoprotein (LDL) and apolipoprotein B (Apo B) concentrations (P<0.05 for pairwise comparisons for both values) in the exenatide groups vs the placebo groups. No significant differences were seen

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	contraceptives for at least 3 months prior to and throughout study			in other lipid parameters evaluated (*P* values not reported). Side effects reported by patients receiving exenatide 10 µg included: nausea (51%), vomiting (13%), diarrhea (9%), constipation (9%), and hypoglycemia (36%) (*P* values not reported). There were 13 (10.1%) withdrawals due to adverse event(s) in the exenatide 10 µg group, compared to 9 (7.2%) in the exenatide 5 µg group and 4 (3.3%) in the placebo group (*P* values not reported). The majority of the events reported were mild-moderate in nature. Serious adverse events were reported in 4% of patients in the exenatide 10 µg group, 3% in the 5 µg group, and 8% in the placebo arm. Such events included a myocardial infarction in a patient in the exenatide group and one patient in the placebo group who experienced clinical manifestations of coronary artery disease.
DeFronzo et al[16] Exenatide 5 µg SQ BID in addition to their existing metformin therapy vs exenatide 5 µg SQ BID titrated to 10 µg BID after 4 weeks in addition to their existing metformin therapy vs placebo in addition to patients' existing metformin therapy	MC, PC, PG, RCT, TB Type 2 diabetic patients between the ages of 19 and 78 years, treated with metformin (≥1,500 mg/day) for at least 3 months before screening, FPG <240 mg/dL, BMI of 27-45 kg/m^2, HbA_{1c} 7.1%-11.0%, stable weight (± 10%) for 3 months prior to screening, no lab value >25% outside of normal value, and if female, who were postmenopausal, surgically sterile, or using contraceptives for at least 3 months prior to and throughout study	N=336 30 weeks	Primary: Change in HbA_{1c} Secondary: Percentage of patients achieving HbA_{1c}≤7%, change in FPG, weight, and fasting concentrations of insulin, proinsulin and lipids	Primary: Significantly greater reductions in HbA_{1c} were reported with exenatide 10 µg (–0.78%), exenatide 5 µg (–0.40%) vs placebo (+0.08%; *P*<0.002 for pairwise comparison). Secondary: A significantly greater proportion of patients achieved HbA_{1c}≤7% in the exenatide 5 µg (27%) and exenatide 10 µg (40%) groups compared to placebo (11%; *P*<0.01 for pairwise comparison). Significantly greater reductions in FPG were observed with exenatide 5 µg (–7.2 mg/dL; *P*<0.005) and exenatide 10 µg (–10.1 mg/dL; *P*<0.0001) compared to placebo (+14.4 mg/dL). Significantly greater reductions in body weight were noted with exenatide 5 µg (–1.6 kg; *P*<0.05) and exenatide 10 µg at week 30 (–2.8 kg; *P*<0.001) compared to placebo (–0.3 kg). There was not a significant difference in fasting insulin or proinsulin concentrations between the exenatide groups and placebo (*P* values not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				No significant differences in lipid profile were observed between treatment groups (*P* value not reported). Gastrointestinal side effects were most commonly reported with exenatide and included nausea (45%), diarrhea (16%) and vomiting (12%) in the 10 µg treated subjects (*P* values not reported). Hypoglycemia was similar in all treatment groups. Withdrawals due to adverse event(s) occurred with 7.1% of patients in the exenatide 10 µg group, 3.6% in the exenatide 5 µg group and 0.9% in the placebo group (*P* values not reported).
Kendall et al[17] Exenatide 5 µg SQ BID in addition to patients' existing diabetes regimens vs exenatide 5 µg SQ BID titrated to 10 µg BID after 4 weeks in addition to patients' existing diabetes regimens vs placebo in addition to patients' existing diabetes regimens All subjects continued prestudy metformin regimen. To standardize	DB, MC, PC, PG, RCT Type 2 diabetic patients between the ages of 22-77 years, treated with maximally effective doses of metformin (≥1,500 mg/day) and a sulfonylurea (4 mg/day glimeperide, 20 mg/day glipizide, 10 mg/day glipizide XL, 10 mg/day glyburide, 6 mg/day micronized glyburide, 350 mg/day chlorpropamide, 500 mg/day tolazamide, or 1,500 mg/day tolbutamide) for at least 3 months before screening, FPG <13.3 mmol/L, BMI 27-45 kg/m^2, HbA_{1c} 7.5%-11.0%, stable weight (±10%) for 3 months prior to screening, no lab value >25% outside of normal value,	N=733 30 weeks	Primary: Change in HbA_{1c} Secondary: Change in FPG and postprandial plasma glucose, and body weight	Primary: A significantly greater reduction in HbA_{1c} was noted with exenatide 5 µg (–0.55 ± 0.07%) and exenatide 10 µg (–0.77 ± 0.08%) vs placebo (+0.23 ± 0.07%; *P*<0.001 for pairwise comparison). Secondary: A significantly greater reduction in FPG was observed with exenatide 5 µg (–0.5 ± 0.2 mmol/L) and exenatide 10 µg (–0.6 ± 0.2 mmol/L) compared to placebo (+0.8 ± 0.2 mmol/L; *P*<0.0001 for pairwise comparison). A significantly greater reduction in postprandial glucose was observed with exenatide 5 µg (*P*=0.009) and exenatide 10 µg (*P*=0.0004) compared to placebo. Significantly greater reduction in body weight was noted with exenatide 5 µg (–1.6 ± 0.2 kg) and exenatide 10 µg at week 30 (–1.6 ± 0.2 kg) vs placebo (–0.9 ± kg; *P*≤0.01). Nausea was the most commonly reported adverse event and was observed in 117 (48.5%) of the exenatide 10 µg patients, in 96 (39.2%) of the exenatide 5 µg patients, and in 50 (20.6%) of the placebo-treated patients (*P* values not reported). A higher incidence of hypoglycemia was reported with exenatide. Hypoglycemia was reported in 67 (27.8%) of the exenatide 10 µg patients, in 47 (19.2%) of the exenatide 5 µg patients, and in 31 (12.6%) of the placebo-treated patients (*P* values not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
sulfonylurea use, subjects were randomized to either maximally effective or minimum recommended sulfonylurea dose.	and if female, who were postmenopausal, surgically sterile, or using contraceptives for at least 3 months prior to and throughout study			
Ratner et al[18] At the start of this uncontrolled open-label extension study after the original placebo controlled trial[16], all patients received exenatide 5 µg BID for 4 weeks, followed by exenatide 10 µg BID for the duration of the study All patients remained on their existing metformin regimens.	ES, MC, OL Type 2 diabetic patients enrolled in the exenatide treatment groups of a previous 30-week, double-blind, placebo-controlled trial (DeFronzo et al, above)[16] who chose to participate in this extension study	N=150 52-week extension (82-week total duration)	Primary: Changes from baseline in HbA_{1c}, body weight and lipids of the completer cohort (those patients who completed 82 weeks of exenatide therapy), and total cohort (intent-to-treat population) Secondary: Proportion of patients in the completer cohort with baseline HbA_{1c}>7% who achieved an HbA_{1c} of ≤7% and reduction of weight after stratification by baseline BMI and safety data	Primary: At week 30, the completer cohort had significant reductions in HbA_{1c} from baseline of –1.0 ± 0.1%. At week 82, the change from baseline was –1.3 ± 0.1% (95% CI, –1.5 to –1.0%; *P*<0.05). For the total cohort, the change from baseline at week 30 was –0.7 ± 0.1% (CI, –0.8 to –0.5%; *P*<0.05) and at week 82 it was –0.8 ± 0.1% (CI, –1.0 to –0.6%; *P*<0.05). At week 30, the completer cohort had significant reductions in body weight from baseline of –3.0 ± 0.6 kg. At week 82, the change from baseline was –5.3 ± 0.8 kg (CI, –7.0 to –3.7 kg; *P*<0.05). For the total cohort, the change from baseline at week 30 was –2.3 ± 0.4 kg and at week 82 it was –4.3 ± 0.6 kg (CI, –5.5 to –3.2 kg; *P*<0.05). At the end of 82 weeks, the completer cohort group experienced significant reductions from baseline in Apo B, –5.2 mg/dL (CI, –10 to –0.22 mg/dL); a reduction in triglycerides, –73 mg/dL (CI, –107 to –39 mg/dL); and an increase in high-density lipoprotein (HDL) +4.5 mg/dL, (CI, +2.3 to +6.6 mg/dL). *P* values were not reported. Secondary: At the end of weeks 30 and 82, the proportion of patients in the completer cohort whose baseline HbA_{1c} was >7% and who achieved an HbA_{1c} of ≤7% was 46% (week 30) and 59% (week 52). *P* values were not reported. Patients in the completer cohort whose baseline BMI of ≥30 kg/m^2 experienced a greater reduction of weight (–6.9 ± 1.1 kg) compared to those whose baseline BMI was <30 kg/m^2 (–2.3 ± 0.8 kg). *P* values were not reported. The following side effects were experienced by patients in the total cohort:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				nausea (14%–33%), upper respiratory tract infections (3%-10%), diarrhea (3%-7%), vomiting (1%-5%), and dizziness (2%-6%). *P* values were not reported.
Riddle et al[19] At the start of this uncontrolled open-label extension study after the original placebo controlled trials[15,17], all patients received exenatide 5 µg BID for 4 weeks, followed by exenatide 10 µg BID for the duration of the studies All patients remained on their sulfonylurea and/or metformin regimens throughout the extension phase study. Sulfonylurea dosing changes were made at the discretion of the investigators.	ES, MC, OL Type 2 diabetic patients enrolled in the exenatide treatment groups of 1 of 2 previous 30-week, placebo-controlled trials (Buse et al and Kendall et al, above)[15,17] who chose to participate in this extension phase study	N=401 52-week extension (82-week total duration)	Primary: Changes in HbA_{1c} from baseline, and FPG levels in the completer cohort (those patients who completed 82 weeks of exenatide therapy), and total cohort (intent-to-treat population) Secondary: Change of weight from baseline, changes in HbA_{1c} and weight stratified by baseline HbA_{1c} and BMI	Primary: At week 30, the completer cohort experienced significant reductions in HbA_{1c} from baseline of –0.8 ± 0.1% for the patients in the original exenatide 5 µg arm and –1.0 ± 0.1% for those in the original 10 µg arm. At week 82, the change from baseline was –1.0 ± 0.1% (95% CI, –0.9 to –1.2%). For the total cohort group, change from baseline at week 82 was –0.7 ± 0.1% (CI, –0.8 to –0.5%); *P* values were not reported. Results from 30 weeks were not reported. At week 30, the completer cohort observed a change from baseline in FPG levels of –0.52 ± 0.16 mmol/L. At week 82, the change from baseline in FPG levels was –0.62 ± 0.19 mmol/L (*P* values not reported). FPG levels for the total cohort were not reported. Secondary: At week 30, the completer cohort group showed changes in body weight from baseline of –1.4 ± 0.3 kg for the original exenatide 5 µg group and –2.1 ± 0.3 kg for the original 10 µg group. At 82 weeks, the change from baseline was –4.0 ± 0.3 kg (95% CI, –4.6 to –3.4 kg). The total cohort showed weight changes from baseline of –3.3 ± 0.2 kg (CI, –2.8 to –3.7 kg). *P* values were not reported. At week 82, patients in the completer cohort who had a baseline BMI ≥30 kg/m^2 experienced a greater reduction in mean weight from baseline of –4.4 ± 0.4 kg, compared to –3.2 ± 0.5 kg for patients with a baseline BMI<30 kg/m^2 (*P* values not reported). Of the patients in the completer cohort who had a baseline HbA_{1c} of >7%, 44% achieved an HbA_{1c} of ≤7% at week 82. Those patients with a baseline HbA_{1c} ≥ 9% experienced a greater reduction (–1.9 ± 0.2%) than those with a baseline HbA_{1c}<9% (–0.7 ± 0.1%); *P* values were not reported. The most common reasons for withdrawal during the open-label extension studies were administrative (study site closure) (12%), withdrawal of consent

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				(11%), and adverse events (7%). *P* values were not reported. In the total cohort of this extension phase, nausea and hypoglycemia were reported in ranges of 14%-27% and 8%-15% of patients, respectively (*P* values not reported.)
Blonde et al[20] At the start of the uncontrolled open-label extension studies after the original placebo controlled trials[15-17], all patients received exenatide 5 µg BID for 4 weeks, followed by exenatide 10 µg BID for the duration of the studies[18,19] All patients remained on their sulfonylurea and/or metformin regimens throughout the extension phase studies. Sulfonylurea dosing changes were made at the discretion of the investigators.	IA, MC, OL Interim analysis of data pooled from type 2 diabetic patients previously enrolled in the exenatide treatment groups of 1 of 3 previous 30-week, placebo-controlled trials (Buse et al, DeFronzo et al, and Kendall et al, above)[15-17] and chose to participate in the extension phase studies (Ratner et al and Riddle et al, above)[18,19]	N=551 52-week extension (82-week total duration)	Primary: Change in HbA_{1c} from baseline and safety in the completer cohort (those patients who completed 82 weeks of exenatide therapy), and total cohort (intent-to-treat population) Secondary: Change from baseline for FPG and weight, changes for weight and HbA_{1c} stratified by baseline BMI and HbA_{1c}, and change in lipids	Primary: At week 30, the completer cohort experienced significant reductions in HbA_{1c} from baseline of –0.9 ± 0.1% and this reduction was maintained at week 82, with a change from baseline of –1.1 ± 0.1% (95% CI, –1.0 to –1.3%). The total cohort observed change from baseline at week 82 was –0.8 ± 0.1% (95% CI, –0.6 to –0.9%). *P* values were not reported. Of the 551 intent-to-treat population, 314 (57%) completed the extension study. Reasons for withdrawal included withdrawal of consent (11%), adverse events (7%), loss of glucose control (4%) and other (21%). *P* values were not reported. In the total cohort of this extension phase, nausea and hypoglycemia were reported in ranges of 14% to 29% and 7% to 12% of patients, respectively (*P* values not reported). Secondary: At week 30, the completer cohort observed a change from baseline in FPG levels of –0.7 ± 0.1 mmol/L. At week 82, the change from baseline in FPG levels was –0.9 ± 0.2 mmol/L (*P* values not reported). The total cohort FPG levels were not reported. At week 30, the completer cohort group experienced changes in body weight –2.1 ± 0.2 kg from baseline and at 82 weeks, the change from baseline was –4.4 ± 0.3 kg (CI, –3.8 to –5.1 kg). At week 82, the total cohort experienced weight changes from baseline of –3.5 ± 0.2 kg (CI, –3.1 to –4.0 kg; *P* values not reported). At 82 weeks, patients in the completer cohort who had a baseline BMI ≥40 kg/m^2 experienced a reduction in mean weight from baseline of –7 kg, compared to –2 kg for patients with a baseline BMI<25 kg/m^2 (*P* values not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				In the completer cohort, of those patients whose baseline HbA_{1c} was >7%, 39% and 48% achieved an $HbA_{1c}\leq 7\%$ at weeks 30 and 82, respectively. At week 82, a greater reduction in HbA_{1c} was observed in those patients who had a baseline $HbA_{1c}\geq 9\%$ (–2.0 ± 0.2%) compared to those with a baseline $HbA_{1c}< 9\%$ (–0.8 ± 0.1%). *P* values were not reported. In the completer cohort, of the lipid levels measured, statistically significant changes were observed in HDL (+4 mg/dL [CI, 3.7 to 5.4 mg/dL]) and triglycerides (–38.6 mg/dL [CI, –55.5 to –21.6 mg/dL]) at week 82 (*P* values not reported).
Buse, Klonoff et al[21] At the start of the uncontrolled open-label extension studies after the original placebo controlled trials[15-17], all patients received exenatide 5 µg BID for 4 weeks, followed by exenatide 10 µg BID for the duration of the studies All patients remained on their sulfonylurea and/or metformin regimens throughout the extension phase studies. Sulfonylurea dosing changes were made by the investigators.	IA, OL Interim analysis of data pooled from type 2 diabetic patients previously enrolled in the exenatide treatment groups of 1 of 3 multicenter, double-blind, placebo-controlled trials (Buse et al, DeFronzo et al, and Kendall et al, above)[15-17] and their open-label extensions (described in Ratner et al, Riddle et al, Blonde et al, above)[18-20] who completed 2 years of treatment with exenatide	N=521 104 weeks (total of 2 years of exenatide treatment)	Primary: Change from baseline for HbA_{1c}, weight, and hepatic biomarkers (aspartate aminotransferase [AST]), alanine aminotransferase [ALT]), adverse events Secondary: Not reported	Primary: At 104 weeks of exenatide treatment, patients in the study experienced a mean reduction in HbA_{1c} of –1.1% (95% CI, –1.3 to –1.0; $P<0.001$) from baseline. At 104 weeks of exenatide treatment, patients experienced a mean reduction in weight of –4.7 kg (95% CI, –5.4 to –4.0; $P<0.001$) from baseline. At 104 weeks of exenatide treatment, patients experienced a significant decrease of –5.3 IU/L (95% CI, –7.1 to –3.5; $P<0.05$) in mean ALT levels from baseline and a decrease of –2.0 IU/L (95% CI, –3.3 to –0.8; $P<0.05$) in mean AST levels from baseline. Adverse events with an overall incidence of ≥10% in the 104 week period were reported with the following percent of patients affected: nausea (8%-39%), upper respiratory tract infections (2%-10%), and hypoglycemia (<1%-13%). *P* values were not reported. Secondary: Not reported
Klonoff et al[22]	IA, OE, OL	N=217	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
At the start of the uncontrolled open-label extension studies after the original placebo controlled trials[15-17], all patients received exenatide 5 µg BID for 4 weeks, followed by exenatide 10 µg BID for the duration of the studies All patients remained on their sulfonylurea and/or metformin regimens throughout the extension phase studies. Sulfonylurea dosing changes were made at the discretion of the investigators.	Interim analysis of data pooled from type 2 diabetic patients previously enrolled in the exenatide treatment groups of 1 of 3 multicenter, double-blind, placebo-controlled trials (Buse et al, DeFronzo et al, and Kendall et al, above)[15-17] and their open-label extensions (described in Ratner et al, Riddle et al, Blonde et al, above)[18-20] who completed 3 years of treatment with exenatide	156 weeks (total of 3 years of exenatide treatment)	Change from baseline for HbA_{1c}, weight, and alanine aminotransferase [ALT]), adverse events Secondary: Not reported	At 156 weeks of exenatide treatment, patients in the study experienced a mean reduction in HbA_{1c} of –1.0 ± 0.1% from baseline (P<0.0001). At 156 weeks of exenatide treatment, patients experienced a mean reduction in weight of –5.3 ± 0.4 kg from baseline (P<0.0001). At 156 weeks of exenatide treatment, patients with elevated ALT levels experienced a significant decrease of –10.4 ± 1.5 IU/L in mean ALT levels from baseline (P<0.0001). The most frequently reported adverse event was mild-to-moderate nausea. Secondary: Not reported
Zinman et al[23] Exenatide 5 µg SQ BID for 4 weeks followed by 10 µg injections BID in addition to existing thiazolidinedione (TZD) regimen (with or without metformin)	MC, PC, RCT Patients between the ages of 21 and 75 years with a stable dose of a TZD (rosiglitazone ≥4 mg/d, or pioglitazone ≥30 mg/d) for at least 4 months before screening, alone or in combination with a stable dose of metformin	N=233 16 weeks	Primary: Change from baseline in HbA_{1c} levels Secondary: Fasting serum glucose levels, body weight, self-monitored blood glucose	Primary: The patients in the exenatide group had a significant decrease in mean HbA_{1c} levels from baseline of 0.89% ± 0.09% (P<0.001), in comparison to an increase of 0.09% ± 0.10% in the placebo group (P<0.001). Secondary: Patients in the exenatide group experienced a significant decrease in mean fasting serum glucose level (–1.59 ± 0.22 mmol/L) compared to those in the placebo group (0.10 ± 0.21 mmol/L), (P<0.001). Patients in the exenatide group had a significant reduction in mean body weight

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo BID in addition to patients' usual TZD doses (with or without metformin)	for 30 days, an HbA_{1c} value between 7.1% and 10.0% at screening, body mass index between 25 kg/m^2 and 45 kg/m^2, and a history of stable body weight (≤10% variation) for at least 3 months before screening		levels, and adverse events	from 97.53 kg (± 1.73 kg) to 95.38 kg (± 0.25 kg) compared to a change of 96.75 kg (± 1.81 kg) to 96.89 kg (± 0.26 kg) in the placebo group. At week 16, the mean difference in body weight reduction between groups was –1.51 kg (*P*<0.001). Patients in the exenatide group experienced significantly lower self-monitored blood glucose profiles at each measurement throughout the day at week 16 compared with baseline measurements (*P*<0.001) and compared to placebo (*P*<0.001). Adverse events that were reported more commonly in the exenatide group vs placebo included: nausea (39.7% vs 15.2%; CI, 12.7 to 36.3), vomiting (13.2% vs 0.9%; CI, 5.2 to 19.5), and dyspepsia (7.4% vs 0.9%; CI, 0.7 to 12.4). (*P* values were not reported.)
Viswanathan et al[24] Exenatide 5 µg SQ BID vs control group (patients who discontinued exenatide therapy within 2 weeks on initiation due to insurance-related, personal, or economic reasons) The dosages of rapid-acting and mixed insulins were reduced by 10% in subjects with HbA_{1c}	RA Obese patients with type 2 diabetes not adequately controlled despite treatment with oral hypoglycemic agents and insulin and whose HbA_{1c} was greater than 7%	N=52 26 weeks	Primary: Change in body weight, HbA_{1c}, insulin dosage Secondary: Change in serum total cholesterol, triglycerides, systolic blood pressure, and high-sensitivity CRP, adverse events	Primary: Patients in the exenatide treatment group experienced a decrease in mean body weight from baseline of 6.46 ± 0.8 kg (*P*<0.001) while the patients in the control group experienced a mean weight gain of 2.4 ± 0.6 kg (*P*<0.001). Patients in the exenatide treatment group experienced a decrease in mean HbA_{1c} from baseline of 0.6 ± 0.21% (*P*=0.007). The patients in the control group experienced a decrease in mean HbA_{1c} from baseline of 8.4 ± 0.5% (*P* value not reported). The exenatide treatment group experienced a decreased requirement for rapid-acting insulins from 50.4 ± 6.7 units to 36.6 ± 5.1 units (*P*<0.02) and for mixed insulins from 72.9 ± 15.6 units to 28.3 ± 14.8 units (*P*<0.02). Insulin requirements for the control group were not reported. Secondary: The exenatide treatment group experienced a decrease in mean serum total cholesterol of 163.9 ± 8.2 mg/dL to 149.8 ± 5.9 mg/dL (*P*=0.03) and the control group experienced a decrease from 168.1 ± 16.3 mg/dL to 144.33 ± 10.39 mg/dL (*P*=0.08). The exenatide treatment group experienced a decrease in mean triglycerides from

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
levels less than 7.5%. Subsequent dosage adjustments were made carefully based on ambient glucose concentrations.				202.5 ± 28.8 mg/dL to 149.9 ± 17.3 mg/dL (*P*=0.01) and the control group experienced a decrease from 182.7 ± 23.9 mg/dL to 171.1 ± 39.2 mg/dL (*P*=0.91). The exenatide treatment group experienced a decrease in mean systolic blood pressure by 9.2 ± 3.3 mm Hg (*P*=0.02). The values for the control group were not reported. Neither the treatment group nor the control group experienced a significant reduction in diastolic blood pressure. The exenatide treatment group experienced a decrease in mean high-sensitivity CRP by 34 ± 14.3% (*P*=0.05). The values for the control group were not reported. Four patients receiving exenatide experienced severe nausea during treatment which led to discontinuation of the drug. Mild nausea was experienced by several other patients who did not interfere with therapy. Hypoglycemia (glucose <60 mg/dL) was rare and did not lead to any hospital admissions. No other adverse events were observed. No *P* values were reported.
Heine et al[25] Exenatide 5 µg SQ BID for 4 weeks, then 10 µg BID in addition to patients' metformin and/or sulfonylurea regimens vs insulin glargine once daily at bedtime (forced insulin glargine titration to fasting blood sugar	OL, RCT Patients between 30-75 years with type 2 diabetes not adequately controlled (defined as HbA_{1c} of 7%-10%) with combination metformin and sulfonylurea therapy at maximally effective doses, BMI between 25 to 45 kg/m^2 and a history of stable body weight (≤10% variation for ≥3 months before screening)	N=551 26 weeks	Primary: Change in HbA_{1c} Secondary: Change in FPG, fasting glucose <100 mg/dL and body weight loss	Primary: At 26 weeks, similar reductions in HbA_{1c} were noted between exenatide and insulin glargine (–1.11%, CI, –0.123 to 0.157; *P* value not reported). Secondary: A significantly reduction in fasting plasma glucose from baseline was observed in the insulin glargine group (–51.5 mg/dL; *P*<0.001). The reduction from baseline in the exenatide group was not significant (–25.7 mg/dL; *P* value not reported). A significant reduction was observed in the insulin group when compared to the exenatide group (CI, 20 to 34 mg/dL; *P* value not reported). A significantly greater proportion of patients taking insulin glargine (21.6%) achieved fasting glucose of <100 mg/dL than those taking exenatide (8.6%; *P*<0.001). A significant weight loss was experienced in the exenatide group (–2.3 kg) compared to a gain of +1.8 kg in the insulin group (CI, –4.6 to –3.5 kg;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
[FBS] <100 mg/dL) in addition to patients' metformin and/or sulfonylurea regimens				*P*<0.001). Similar rates of hypoglycemia were reported with both agents (CI, –1.3 to 3.4 events/patient-year). Exenatide patients had a higher incidence of daytime hypoglycemia (CI, 0.4 to 4.9 events/patient-year; *P* value not reported), and a lower rate of nocturnal hypoglycemia than insulin glargine patients (CI, –2.3 to –0.9 events/patient-year; *P* value not reported). A significantly higher incidence of gastrointestinal side effects, including nausea (57.1% vs 8.6%; *P*<0.001), vomiting (17.4% vs 3.7%; *P*<0.001) and diarrhea (8.5% vs 3%; *P*=0.006), upper abdominal pain (*P*=0.012), constipation (*P*=0.011), dyspepsia (*P*=0.011), decreased appetite (*P*=0.021), and anorexia (*P*=0.002) were reported in the exenatide group vs the insulin group. Withdrawals due to adverse events occurred in 9.5% of exenatide patients vs 0.7% of insulin patients (*P* value not reported).
Secnik Boye et al[26] Exenatide 5 µg SQ BID for 4 weeks, then 10 µg BID in addition to patients' metformin and/or sulfonylurea regimens vs insulin glargine once daily at bedtime (forced insulin glargine titration to FBS <100 mg/dL) in addition to patients' metformin and/or sulfonylurea	MC, OL, RCT Secondary analysis on patients with type 2 diabetes inadequately controlled (defined as an HbA_{1c} between 7% and 10%) with sulfonylurea and metformin therapy at maximally effective doses, enrolled in a previous 26 week study[18]	N=455 26 weeks	Primary: Patient-reported health outcome measures: Diabetes Symptom Checklist-revised (DSC-R), Diabetes Treatment Satisfaction Questionnaire (DTSQ), EuroQol Quality of Life (EQ-5D), Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), Diabetes Treatment Flexibility Score	Primary: Both exenatide and insulin glargine groups experienced a significant improvement from baseline in patient-reported health outcome measures as demonstrated by DSC-R overall scores, DTSQ, EQ-5D and SF-36 scores (*P*<0.05 for all measures). There was not a statistical difference between treatment groups in any of the outcome measures (*P*>0.05 for all measures). Neither the exenatide nor the insulin glargine group experienced a significant improvement in TFS scores (*P*=0.93 for both groups). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
regimens			(TFS) Secondary: Not reported	
Nauck et al[27] Exenatide 5 µg SQ BID for 4 weeks, then 10 µg BID for the remainder of the study in addition to patients' metformin and sulfonylurea treatment vs insulin aspart SQ BID in addition to patients' metformin and sulfonylurea treatment (investigators and/or patients titrated insulin doses for optimal glucose control)	MC, OL, RCT Patients between the ages of 30 and 75 years who had suboptimal glycemic control despite receiving optimally effective metformin and sulfonylurea therapy for ≥3 months, HbA_{1c} levels ≥7.0 and ≤11.0%, a BMI ≥25 and ≤40 kg/m^2, and a history of stable body weight (≤10% variation for ≥3 months)	N=501 52 weeks	Primary: Mean change in HbA_{1c} levels, weight, fasting serum glucose levels, postprandial glucose levels, adverse events Secondary: Not reported	Primary: There was not a significantly different change from baseline in mean HbA_{1c} levels between the exenatide (–1.04%) and insulin aspart groups (–0.89%, 95% CI, −0.32% to 0.01%; *P*=0.067). Patients in the exenatide group experienced a gradual weight loss of –2.5 kg, compared to a gradual weight gain of 2.9 kg in the insulin aspart group, (CI, −5.9 to −5.0; *P*<0.001) at the end of 52 weeks. Patients in both exenatide (–1.8 mmol/L) and insulin aspart (–1.7 mmol/L) groups had a significant decrease in fasting serum glucose compared to baseline (*P*<0.001 for both groups). There was not a significant difference between groups (CI, −0.6 to 0.4; *P*=0.689). Patients in the insulin aspart group had significantly lower mean glucose values at prebreakfast (*P*=0.037), prelunch (*P*=0.004) and 03.00 hours (*P*=0.002). Patients in the exenatide group had a greater reduction in postprandial glucose excursions following morning (*P*<0.001), midday (*P*=0.002) and evening meals (*P*<0.001). The withdrawal rate was 21.3% in the exenatide group and 10.1% in the insulin aspart group. Adverse events that were more commonly reported in the exenatide vs insulin aspart group included: nausea (33.2% vs 0.4%), vomiting (15% vs 3.2%), diarrhea (9.5% vs 2%) and other clinically relevant adverse events (13.4% vs 6.4%). (*P* values were not reported.) Secondary: Not reported
Amori et al[28] Incretin therapy (exenatide,	MA RCTs that reported HbA_{1c} levels in nonpregnant	N=12,996 29 trials	Primary: HbA_{1c} levels Secondary:	Primary: In totoal there were seven studies that evaluated the safety and/or efficacy of exenatide.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
liraglutide*, sitagliptin and vildagliptin*) vs non-incretin-based therapy (placebo or hypoglycemic agent)	patients with type 2 diabetes	Duration varied from 12 to 52 weeks	Fasting plasma glucose, weight, adverse events	There was no significant difference between insulin and exentaide in HbA_{1c} (RR, 1.10; 95% CI, 0.81 to 1.50) or fasting plasma glucose (weighted mean difference 13; 95% CI, -16 to 14). Secondary: Comapred to placebo patients receiving exenatide were more likely to achieve an HbA_{1c} <7% (10% vs 45%; RR, 4.2; 95% CI, 3.2 to 5.5). A significant reduction in weight was seen in the exenatide group compared to placebo (weighted mean difference -1.44; 95% CI, -2.13 to -0.75) and insulin (weighted mean difference -4.76; 95% CI, -6.03 to -3.49).

*Agent not currently available in the United States
Drug regimen abbreviations: BID=twice daily, SQ=subcutaneous, XL=extended release
Study abbreviations: CI=confidence interval, DB=double-blind, ES=extension study, IA=interim analysis, MC=multicenter, OE=open-ended, OL=open-label, PC=placebo-controlled, PG=parallel-group, RA=retrospective analysis, RCT=randomized controlled trial, RR=risk ratio, TB=triple-blind
Other abbreviations: ALT=alanine aminotransferase, AST=aspartate aminotransferase, Apo B=apolipoprotein B, BMI=body mass index, CRP= C-reactive protein, DSC-R=Diabetes Symptom Checklist-revised, DTSQ=Diabetes Treatment Satisfaction Questionnaire, EQ-5D=EuroQol Quality of Life, FBS=fasting blood sugar, FPG=fasting plasma glucose, HbA_{1c}=hemoglobin A1c, HDL= high-density lipoprotein, LDL= low-density lipoprotein, SF-36= Medical Outcomes Study 36-Item Short-Form Health Survey, TFS=Diabetes Treatment Flexibility Score, TZD=thiazolidinedione

IX. Conclusions

Exenatide has demonstrated effectiveness in improving glycemic control within the drug's FDA-approved indications. In clinical trials, exenatide demonstrated the ability to reduce HbA_{1c} by –0.4% to –0.9% in type 2 diabetics not adequately controlled with metformin, a sulfonylurea, a thiazolidinedione, a combination of metformin and a sulfonylurea or a thiazolidinedione, or a combination of these agents with insulin. A recent interim analysis demonstrated maintenance of HbA_{1c} and weight reductions for periods of up to 104 weeks.[21] Exenatide has not been directly compared to oral treatments for type 2 diabetes nor has there been any published data examining the safety and efficacy of exenatide in combination with meglitinides or α-glucosidase inhibitors. Exenatide also has a high incidence of gastrointestinal side effects, particularly nausea. In clinical trials, there was a higher rate of withdrawals in the exenatide-treated groups due to adverse events.[15-18,20] In addition, clinical trials reported that exenatide produces weight loss which may raise concerns for off-label use for weight control.

In direct-comparison trials with insulin therapy, exenatide was shown to be as effective in reducing HbA_{1c} as insulin glargine and insulin aspart. Insulin glargine displayed more favorable fasting blood glucose levels, and patients in the insulin treatment groups experienced significantly less side effects, including nausea and vomiting, than patients in the exenatide treatment groups. A loss of weight was observed in the exenatide-treated patients while the insulin-treated patients gained weight.[25,27] In a secondary analysis evaluating patient-health outcome measures, patients receiving exenatide reported improvements similar to those receiving insulin glargine.[26] According to the product labeling, exenatide is not intended as a substitute for insulin in diabetics requiring insulin therapy.

The ACE/AACE Diabetes Road Map Task Force does not recommend exenatide as a first-line agent. An incretin mimetic (exenatide) is listed as an option for treatment-naïve patients on maximally effective doses of a thiazolidinedione, a sulfonylurea and/or metformin who have an initial HbA_{1c} of 6.5%-8.5% and have not achieved ACE glycemic goals. Exenatide is also listed as an adjunctive therapy option to a thiazolidinedione, a sulfonylurea and/or metformin in treatment experienced type 2 diabetics with a current HbA_{1c} of 6.5%-8.5% and who have not achieved ACE glycemic goals.[10] A recently released treatment algorithm for type 2 diabetes endorsed by the American Diabetes Association and the European Association for the Study of Diabetes did not incorporate the use of exenatide as a therapy option. Though not specific, the rationale provided states that this agent, among others, was not included due to the lower overall glucose-lowering effectiveness and/or limited clinical data. The consensus algorithm does state that the use of this agent may be appropriate in selected patients, which were not specified.[6-7] Currently, the National Institute for Clinical Excellence (NICE) have not incorporated the use of exenatide in their treatment guidelines.[11-12] Also, the International Diabetes Federation (IDF) did not include exenatide in their Global guideline for type 2 diabetes recommendations[4], although in a recently published IDF guideline on the management of postmeal glucose[5], exenatide is listed as an available treatment option, along with the α-glucosidase inhibitors, meglitinides, amylin analogs and dipeptidyl peptidase-4 (DPP-4) inhibitors for postmeal glucose management.

The use of exenatide is not recommended in patients with gastrointestinal disorders or in those with renal impairment (creatinine clearance <30 mL/min) or end-stage renal disease. Also, due to the risk of developing anti-exenatide antibodies, patients receiving exenatide should be monitored for hypersensitivity reactions.[3] In addition, the FDA has recently published an alert to health care providers regarding an association between exenatide and pancreatitis. It is recommended that health care providers monitor their patients closely for any signs and symptoms of pancreatitis and discontinue exenatide if it is suspected.[14]

X. Recommendations

In recognition of exenatide's current labeled indication as 'adjunctive' therapy in diabetic patients who have not achieved target goals using first-line oral agents; its potential risks (eg, pancreatitis); lack of robust long-term safety and efficacy data; and a potential for off-label use as an anorexiant, it is recommended that:

1) Exenatide be made available after Prior Authorization after the following criteria are met:
   - The patient has a diagnosis of diabetes mellitus and
   - The patient is at least 18 years old and
   - The patient has had a documented side effect, allergy, or treatment failure to at least two oral anti-diabetic agents (one medication from two different classes).

Finally, given the product's labeled dosing recommendations and results of clinical dose ranging trials, it is also recommended that:

2) A quantity limit of 1 pre-filled pen per 30 days be employed.

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